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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/583,107	07/17/2007	Tim H. Bruemmendorf	33510-US-PCT	1234

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/583,107	BRUEMMENDORF ET AL.	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 June 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *14-17* is/are objected to.

8)☒ Claim(s) *1-7 and 13-17* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-2 and 15-17, drawn to a method of treating ANY proliferative disease comprising the specific peptide compound N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine, and ANY hypusination inhibitor.

II. Claims 3, drawn to a method of treating a warm-blooded animal having leukemia, particularly Imatinib-resistant leukemia, comprising administering to the animal ANY hypusination inhibitor, in a quantity which is therapeutically effective against leukemia and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.

III. Claims 4-7 and 13-14, drawn to a combination or pharmaceutical composition comprising the specific peptide compound N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine, and ANY hypusination inhibitor, for treating ANY proliferative disease.

NOTE: An Open Invitation for Interview to Discuss:

Presently Claimed Method's of Use as read in light of the Specification Support for Enablement (35 USC 112 1st para)

It would appear based on Applicant's present description (absent further evidence by 37 CFR 1.132 Declaration – since Applicant expressly indicated twice in the results section on pages 18-20 "(data not shown)") that the subject matter as presently claimed, is of a hypothetical/theoretical future, potential treatment for proliferative diseases such as CERTAIN-TYPES of leukemia (e.g. Bcr-Abl+, but not Bcr-Abl neg.; as shown on p. 19), as evidenced by Applicant's admitted results on page 19:

> eIF5a **seems to be essential** for proliferation of cells, since disruption of hypusine synthesis leads to cell cycle arrest. The minor human isoform, eIF5a2, has been **suspected** to be an oncogene. It is speculated that eIF5a facilitates transport and/or translation of specific mRNAs. Thus, Bcr-Abl induced upregulation of eIF5a **could potentially play a role in the increased cellular proliferation observed in Bcr-Abl positive leukemia's.** Similarly, inhibition of Bcr-Abl **could exert** its anti-proliferative effect via inhibition of eIF5a expression.
>
> [ ]
>
> **"Our findings support the central role of eIF5A for cell cycle control in Bcr-Abl-positive leukemia's and points to this protein as being a potential new target for future therapies."**

If so, and there is no new evidence to support enablement of the treating a proliferative disease, **the Examiner is open to Applicant amending the claims to inhibiting that pathway or peptide (e.g. eIF5A) by the use of a hypusination inhibitor such as Ciclopirox or a combination therewith, e.g. ciclopirox with Imatinib – noted as the only compounds tested alone or in combination; which is not presently claimed independently.**

If Applicant is not open to the above, the further elections below, based on the subject matter as claimed, are required. Of which the Examiner suggests, in the interests of compact

prosecution and advancement toward potential allowable subject matter, that Applicant proactively address/provide further evidence of enablement (35 USC 112 1st para) of how a compound alone (ciclopirox) or in combination (ciclopirox with Imatinib) has been shown to treat one or more proliferative diseases, such as that of present claim 3, Bcr-Abl + Imatinib-resistant leukemia (e.g. in the accepted mouse model).

Lack of Unity

An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) a product and a process specially adapted for the manufacture of said product; or (2) a product and a process of use of said product; or (3) a product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) a process and an apparatus or means specifically designed for carrying out the said process; or (5) a product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application and the first recited invention of each of the other categories related thereto will be considered as the main invention in the claims, see PCT Article 17(3)(a) and 1.476(c).

No 'Special' Technical Feature or Markush Group

Group I requires the 'technical feature' of the specific peptide compound N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine. As well as in combination with ANY hypusination inhibitor (a genus of compounds well known in the art, thus not a 'special' technical feature). Thus, even if the the specific peptide compound N-(5-[4-

(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine was not known in the art, whereby it may rise to being the required 'special' technical feature; it is a moot issue, since Group II does not require and share this 'technical feature'. **Thus all the groups do not share a 'special' technical feature and the claims lack unity of invention.**

I. Requirement for Election of a Single Hypusination Inhibitor, if Group I-III is elected as the Invention

The invention is drawn to the use of any hypusination inhibitors. Hypusination inhibitors are structural distinct compounds, as evidenced by the 6 distinct examples expressly claimed (claims 15-17): deferozamine, **ciclopirox** [ONLY 1 TESTED, p. 18-20 specification], deoxyspergualin, deferiprone, GC-7, and 4-[3,5-bis(2-hydroxyphenyl)-[1,2,4]triazol-1-yl]benzoic acid. Any one of which would require an individual sequence and/or structure search, as there is no overlapping coextensive search possible. The search of each and every peptide would thus constitute an undue search burden; *as art on one would not read on another (OR THE COMBINATION, as in Groups I and III* with the peptide compound N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine*), absent express evidence to the contrary by Applicant's admission.* **Therefore, irrespective of which Group I-III is elected as the invention, Applicant must elect a single hypusination inhibitors peptide (e.g. ciclopirox; as in claim 17), as the invention (not species), to which the elected Invention group will be searched.**

This requirement is not to be taken as an election of species, but rather as an election of a single invention, since each compound is assumed to be a patentably distinct invention, in the absence of evidence to the contrary.

II. Requirement for Election of a Single Proliferative Disease, if Group I or III is Elected as the Invention

Groups I and III are drawn to treating (or by functional language in the product) ANY proliferative disease. The breadth of this label is infinite. It is well known in the 40+ year fight against proliferative diseases such as cancer generally (or even Group II's expressly claimed leukemia or imatinib-resistant leukemia), that there are a myriad of specific proliferative diseases let alone the entire genus, that are each unique in what may or may not work to treat any specific type. Absent evidence to the contrary that any of the specific combination may treat more than 1 type or proliferative disease, e.g. Imatinib-resistant leukemia, which was not uncovered in the specification, Applicant must elect a single specific type of proliferative disease (again, e.g. Imatinib-resistant leukemia), **as the invention (not species) to be treated by the elected hypusination inhibitor in combination with the peptide compound N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine, as the invention (not species).**

It is noted that there were no Figures/Drawings in the specification to display test data; but the last 3 pages of the specification (p. 18-20) provide testing of the **hypusination inhibitor ciclopirox with Imatinib, in the affecting eIF5A** (which Applicant describes on specification p. 19, bottom (noted below), based on Applicant's studies: "**the central role of eIF5A for cell**

cycle control in Bcr-Abl-positive leukemia's and points to this protein as being a potential new target for future therapies (emphasis added by Examiner). And assert that a SYNERGISTIC effect was found with this combination.

However, it is noted that **ciclopirox with Imatinib** is not a combination claimed (unless Imatinib is also know by the peptide formula: N-(5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl)4-(3-pyrimidine-amine; see claim 1):

Example 3

eIF5A and Synergistic Effects of Imatinib and Ciclopirox

While the underlying mechanisms of action are poorly understood, it has been suggested that the activity of Interferon-alpha and Ara-C and other drugs that are currently being used for the treatment of CML may involve inhibition of hypusination of eIF5A.

Hypusination is induced stepwise by two mechanisms. In a first step, catalyzed by the enzyme deoxyhypusine-synthase, deoxyhypusine intermediates are formed by NAD-dependent transfer of 4-aminobutyl to lysine residues of the eIF5a precursor. The second step generates the active form of eIF5a and involves the hydroxylation of the side chain of the deoxyhypusine intermediates by a second enzyme called deoxyhypusine hydroxylase.

eIF5a **seems to be essential** for proliferation of cells, since disruption of hypusine synthesis leads to cell cycle arrest. The minor human isoform, eIF5a2, has been **suspected** to be an oncogene. It is speculated that eIF5a facilitates transport and/or translation of specific mRNAs. Thus, Bcr-Abl induced upregulation of eIF5a **could potentially play a role in the increased cellular proliferation observed in Bcr-Abl positive leukemia's.** Similarly, inhibition of Bcr-Abl **could exert** its anti-proliferative effect via inhibition of eIF5a expression.

In order to test this hypothesis, we investigated whether additive or even synergistic effects could be detected by treating Bcr-Abl positive leukemia cells with hypusination inhibitors and Imatinib. **Specifically, we analyzed potential synergistic effects between Imatinib and ciclopirox** on Bcr-Abl positive K562 cells by measuring cellular cytotoxicity and apoptosis.

Using a tetrazolium-based MTT assay, we quantified growth inhibition in K562 cells after 24 h of exposure to ciclopirox or Imatinib alone as well as to a combination of both drugs in the K562 cells and also in Bcr-Abl-negative HL-60 cells. The cells were treated with ciclopirox or Imatinib at increasing concentrations as follows: K562 cells were

treated with 0, 0.33, 1, 3, 9, 27, 81 IJM ciclopirox and/or 0, 0.01,0.037, 0.11, 0.33, i.0, 3.0 IJM Imatinib; HL-60 cells were treated with 0, 0.33, 1, 3, 9, 27, 81 IJM ciclopirox and/or 0, 0.33, 1, 3, 9, 27, 81 IJM Imatinib.

Whereas an anti-proliferative effect was detected with ciclopirox alone, data indicate that the combination of Imatinib and ciclopirox were significantly synergistic on cellular cytotoxicity in Bcr-Abl positive K562 cells. In contrast, no synergistic effect with Imatinib was observed when the Bcr-Abl negative myeloid leukemia cell line HL60 was treated with both drugs as Bcr-Abl-negative HL-60 cells were not affected by this combination. Results are representative of at least 3 independent experiments (data not shown).

Apoptosis was also measured after 24 h by flow cytometric evaluation of hypodiploid nuclei as described in above Methods. In these experiments, K562 and HL-60 cells were treated with ciclopirox at increasing concentration (0 to 81 IJ .M.or with 0.15 IJM Imatinib and ciclopirox at increasing concentration (0 to 81 IJM). **Data indicate that Imatinib sensitizes Bcr-Abl-positive K562 cells but not Bcr-Abl negative HL-60 cells to ciclopirox-induced apoptosis. Results are representative of at least 3 independent experiments (data not shown).**

Our findings support the central role of eIF5A for cell cycle control in Bcr-Abl-positive leukemia's and points to this protein as being a potential new target for future therapies. Interestingly, among the substances known to inhibit hypusination, deferoxamine (iron overload agent) and ciclopirox (topically used anti-fungal) are clinically approved drugs with an acceptable toxicity profile. Thus, based on the results reported herein, it is contemplated that clinical treatment strategies combining hypusination inhibitors with/without Imatinib could be used to reduce the development of clinical resistance to Imatinib in Bcr-Abl positive leukemia's, as well as other disease entities treated with Imatinib.

This requirement [ELECTION OF A SINGLE PROLIFERATIVE DISEASE] is not to be taken as an election of species, but rather as an election of a single invention, since each compound is assumed to be a patentably distinct invention, in the absence of evidence to the contrary.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CRF 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

In re Ochiai/Brouwer Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claim Objections

Claims 14-17, line 2, are objected to because of the following informalities: the term "in" following the phrase "claim 1" needs to be deleted for grammatical correctness.

Appropriate correction is required.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 12/16/2009

/Maury Audet/
Examiner, Art Unit 1654
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